Managing the Aftermath
The WHI experience of stopping the estrogen plus progestin trial

Garnet Anderson, PhD
Andrea LaCroix, PhD
WHI Clinical Coordinating Center
Fred Hutchinson Cancer Research Center

Overview

- Critiques and responses
- Impact on other groups
  - Other studies
  - Pharmaceutical company
  - Other government agencies

Critiques

- Approximately 60 letters to the editor
- Letters and response required 7 pages of JAMA
- Many common themes

Issues in responding:

- Advantage in having responses published
- Readership of letters to the editor likely small
- Value of providing new data analyses in response

WHI studied the wrong women

- They were too old—this is not how hormones are used in practice.
- They had pre-existing disease.
- They were too fat.

Response:

- Subgroup analyses do not suggest that younger, leaner or clinically healthier women were protected from adverse effects

WHI subgroup analyses were inadequate

- Data were not presented
- Subgroup comparisons were underpowered

Response:

- More detail has/will appear in subsequent papers
- Subgroup tests were performed to look for interactions, not to examine whether we could detect main effects within each subgroup

WHI studied the wrong preparation

- This was not the right progestin.
- This was not the right dose.

Response:

- Continuous E+P chosen to minimize bleeding.
- Intermediate outcome trial data were supportive.
- These were the agents underlying most observational studies showing CHD benefit.
- PremPro was prescribed to 6 million women in the US during the previous year.
- PremPro was provided to the NIH at no charge.

The trial was stopped too early

- Nothing was significant.
- Longer follow-up is needed.

Response:

- Monitoring analyses based on more sophisticated (weighted) statistics
- Presentation provided unweighted hazard ratios and confidence intervals because
  - Familiar
  - Quantitative estimate of effect sizes
  - Were more appropriate for primary outcome

The trial was stopped too early

Response:

- Nominal confidence intervals were shown because
  - Familiar
  - Can be compared to other studies
  - Interpretable individually as having 95% chance of covering the true HR
- Adjusted confidence intervals were shown because
  - Control overall experimental error by accounting for multiple diseases, multiple analyses over time;
  - Though conservative, they make the point that caution must be used in interpreting analyses with these multiplicities

The trial was stopped too early

Response:

- Surveillance will continue through 2005 with existing funds
- WHI has proposed to continue follow-up for 5 more years, without additional intervention

The trial was stopped too late

- Adverse effects on cardiovascular outcomes were identified in late 1999

Response:

- Participants were informed in early 2000 and early 2001 about adverse effects on heart attacks, strokes and blood clots.

MedGen Med's Selection of the Top 10 Medical / Health Stories of 2002

1. The demise of postmenopausal hormone therapy
2. Molecularly targeted therapies come of age in oncology
3. Breast-conserving surgery: final results
4. The narrowing gap between coronary stents and cardiac surgery
5. Intensive insulin therapy in critically ill patients
6. The mouse genome sequenced
7. Complete genome sequence for malaria mosquito
8. HPV vaccination: a first step toward infection control
9. Proving the obvious--more nurses means better patient care
10. Another malpractice crisis in the United States

Impact on other groups

Impact on other studies

- WHI Estrogen Alone Trial
  - Many efforts by WHI to communicate
    - E+P results
    - WHI investigators do not know whether the results for E+P apply to estrogen alone
    - Women need clear answers to the same questions of estrogen alone
    - The DSMB has recommended that the estrogen trial continue
    - Finding these answers depends on their continued participation
  - Continuation is difficult in the face of discouraging news from the parallel trial

Impact on other studies

- WHI ancillary studies in hormone trials
  - WHIMS, the WHI Memory Study
  - WHI-SE, the WHI Sight Examination study
  - Both designed to look at E+P and E-alone trials in a pooled analysis
    - Each has chosen to analyze E+P results now
    - Future follow-up for these studies now rests on finding another sponsor

Impact on other studies

- WISDOM—sister trial of hormone therapy in the UK, Australia
  - Funded by MRC
  - Using the same regimens (Premarin and PremPro)
  - Slightly different design, with most women on E+P vs placebo
  - Still early in the recruitment phase

Impact on other studies

- WISDOM
  - Mid-July trial steering and monitoring committees vote to continue
  - September, MRC seeks information from WHI
  - October 23, WISDOM is halted
    - "In the light of the new evidence and the slow recruitment to date, WISDOM was considered unlikely to provide substantial evidence to influence clinical practice in the next ten years."

Wyeth role in WHI hormone trials

- Provided hormone pills (active and placebo) for the trials
- Funded two ancillary studies,
  - WHIMS
  - WHI-SE
- Had representatives at open sessions of Steering Committee meetings
- Informed of E+P findings on July 3, 2002

Impact on Wyeth

Impact on Wyeth

- Issued a letter to all physicians
- Changed package insert for
  - PremPro
  - PremPhase
  - Premarin

Impact on Wyeth

- Decided not to further fund
  - WHIMS
  - WHI-SE
- Requested all data from the E+P trial
- Requested advanced copies of all subsequent papers

Response to Wyeth

- November 2002, WHI provided data from JAMA 2002 paper
- February 2003, WHI provided additional data
- May 2003, WHI agreed to provide papers in final form just prior to publication

Impact on NIH

- Many hormone studies underway through various institutes
- Pressure on NIH to shape the message
- Criticism of dissemination plan

Hormone Therapy Workshop

- Sponsored by HHS/NIH, with participation of FDA in October 2002
- Summary of the many hormone studies underway, including
  - Current status
  - New or emerging results
  - Support for
    - Lack of benefit for cardiovascular disease
    - Increase in breast cancer

Hormone Therapy Workshop

- Many position statements offered with a tremendous diversity of views
  - Professional organizations
  - Health care providers
  - Academic researchers
  - Industry
  - Consumer representatives
  - Lobbyists

Impact on FDA

- FDA notified on July 5
- Responsibilities were not well-known or appreciated by the WHI investigators
- Ongoing analysis requests

Response by the FDA

- Revised labeling including
  - risks
  - consideration of alternative therapies
- Retracted previous advice to women and health care providers
- Issued revised guidance

Repercussions for FDA

- Raised issues regarding
  - Specific preparations or class effects
  - Approval for new indications for these agents (e.g., osteoporosis prevention)
  - Approval for the same indications for other agents (e.g., menopausal symptoms)
  - Use of observational data to support drug approval considerations

Summary statement

- Elias Zerhouni, NIH Director
  - "The announcement about the decision to stop the combination HT arm of the WHI study, based on the reported results, has caused concern proportionate to the strength of the dogma being overturned by those findings."

Kirschtein R., Menopausal Hormone Therapy: Summary of a Scientific Workshop. Ann Int Med 2002.

Summary statement on preventive medicine

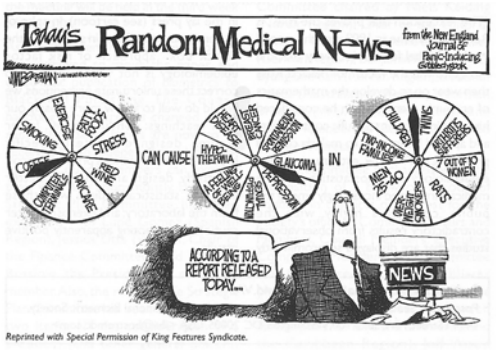
"Without evidence from positive randomized trials, we cannot justify soliciting the well to accept any personal health intervention. There are simply too many examples of the disastrous inadequacy of lesser evidence as a basis for individual interventions among the well…"

Sackett D., The Arrogance of Preventive Medicine. CMAJ 2002;167:363-364.

Summary statement

The low esteem accorded epidemiology and biostatistics in some medical circles, and increasingly among the public, correlates highly with the contradictory results from observational studies that are displayed so prominently in the lay press…

Breslow N. Biometric Bulletin 2002;19:1-2.



Summary statement

- To correct these unfortunate perceptions, we would do well to follow more closely our own teachings:
- conduct larger, fewer studies designed to test specific hypotheses;
- follow strict a priori protocols for study design and analysis;
- better integrate statistical findings with those from the laboratory,
- and exercise greater caution in promoting apparently positive results.